Introduction

THE GLOBAL HIV/AIDS PANDEMIC

The impact of the global HIV pandemic is profound, affecting families, agriculture and famine, business, health care, education, and national economic growth. It is the deadliest epidemic of our generation. The United Nations General Assembly's Declaration of Commitment on HIV/AIDS states "...the global HIV/AIDS epidemic, through its devastating scale and impact, constitutes a global emergency and one of the most formidable challenges to human life and dignity, as well as to the effective enjoyment of human rights, which undermines social and economic development throughout the world and affects all levels of society—national, community, family, and individual."[1] The AIDS epidemic will continue to have devastating consequences around the world for decades to come for virtually every sector of society.

Group	People Newly Infected in 2004	People Living with HIV/AIDS in 2004	AIDS Deaths in 2004
Adults *Women*	4.3 million	37.2 million *17.6 million*	2.6 million
Children	640,000	2.2 million	510,000
Total	4.9 million	39.4 million	3.1 million

Source: UNAIDS

[1] "The Impact of AIDS" (Department of Economic and Social Affairs, United Nations, 2004).

A new United Nations report states: "The disease has such a staggering impact because it weakens and kills many people in their young adulthood, the most productive years for income generation and family caregiving. It destroys families, eliminating a whole generation crucial for the survival of the younger and older persons in society."[2] A recent article stated that: "The spread of HIV/AIDS through Eurasia, in short, will assuredly qualify as a humanitarian tragedy—but it will be much more than that. The pandemic there stands to affect, and alter, the economic potential—and by extension, the military power—of the region's major states....Over the decades ahead, in other words, HIV/AIDS is set to be a factor in the very balance of power within Eurasia—and thus in the relationship between Eurasian states and the rest of the world."[3] Dramatic increases in HIV infection also are occurring in Eastern Europe, Central Asia, Latin America, and the Caribbean.

HIV has already infected more than 60 million people around the world, and AIDS has surpassed tuberculosis (TB) and malaria as the leading infectious cause of death worldwide.[4] Curbing the transmission of HIV from infected mother to infant is an especially compelling challenge in resource-poor countries. The coexistence of other endemic diseases widely prevalent in developing countries, such as respiratory and gastrointestinal infections, complicates treatment and poses additional problems for medical personnel caring for HIV-infected individuals.

THE EPIDEMIC IN THE UNITED STATES

The HIV/AIDS epidemic in the United States continues to expand.[5] [6] [7] In addition, use of antiretroviral therapy (ART) is now associated with a series of side effects and long-term complications that may have a negative impact on mortality rates. HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people over 50 years of age.[8] The appearance of multi-drug-resistant strains of HIV presents an additional serious public health concern.[9] [10] [11] These data forebode an epidemic of even greater magnitude in the coming years. According to CDC reports, approximately one-quarter of the HIV-infected population in the United States also is infected with hepatitis C virus (HCV). HIV/HCV coinfection is found in 50

[2] Ibid.

[3] "The Future of AIDS," Foreign Affairs, November/December 2002.

[4] "Report on the Global HIV/AIDS Epidemic: July 2002" (UNAIDS/WHO, Geneva, Switzerland, 2002).

[5] "Cases of HIV Infection and AIDS in the United States, 2003," HIV/AIDS Surveillance Report (CDC, 2004).

[6] "Centers for Disease Control and Prevention HIV Prevention Strategic Plan Through 2005" (CDC, 2001).

[7] "Cases of HIV Infection and AIDS in the United States, by Race/Ethnicity, 1998-2002," HIV/AIDS Surveillance Supplemental Report (CDC, 2004).

[8] "Characteristics of Persons Living with AIDS and HIV, 2001," HIV/AIDS Surveillance Supplemental Report (CDC, 2003).

[9] N. Loder, Nature 407, 120 (2000).

[10] H. Salomon et al., AIDS 14, 17 (2000).

[11] "World Health Report on Infectious Diseases: Overcoming Antimicrobial Resistance" (WHO, Geneva, 2000).

to 90 percent of injecting drug users (IDUs). HCV progresses more rapidly to liver damage in HIV-infected persons and may also impact the course and management of HIV infection, as HIV may change the natural history and treatment of HCV.[12]

AIDS disproportionately affects African Americans and Hispanics. "According to CDC figures for 2003, approximately 60 percent of newly infected women were African American and 20 percent were Hispanic. Among newly infected men, approximately 40 percent were African American and 22 percent were Hispanic."[13]

THE NIH AIDS RESEARCH PROGRAM

The NIH response to this epidemic requires a unique and complex multi-Institute, multi-disciplinary, global research program. The NIH has developed a comprehensive biomedical and behavioral research program to better understand the basic biology of HIV, develop effective therapies to treat and control HIV disease, and design interventions to prevent new infections from occurring. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of the NIH Institutes and Centers (ICs). This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that research dollars are invested effectively and efficiently. It is the unique role of the Office of AIDS Research (OAR), part of the Office of the Director, to plan and coordinate all AIDS-related research across the NIH, thus allowing the NIH to pursue a united research front against the global AIDS epidemic.

Program Assessment Rating Tool (PART): Assessment of NIH AIDS Program

The NIH AIDS program received an overall score of 83 in the Federal Office of Management and Budget's FY 2005 Program Assessment Rating Tool (PART). This score included a 100 percent in the Program Purpose and Design section. The PART demonstrated that the NIH provides effective scientific coordination and management of this diverse AIDS research portfolio through a comprehensive planning and budget development process, which was utilized to develop the FY 2006 budget request. The NIH is enhancing collaboration, minimizing duplication, and ensuring that research dollars are invested in the highest priority areas of scientific opportunity that will allow the NIH to meet its scientific goals.

[12] "Frequently Asked Questions and Answers About Coinfection with HIV and Hepatitis C Virus" (CDC, 2002).

[13] "Cases of HIV Infection and AIDS in the United States, 2003," HIV/AIDS Surveillance Report (CDC, 2004).

OVERVIEW OF THE PLAN

OAR develops an annual *NIH Plan for HIV-Related Research* that is based on the most compelling scientific priorities that will lead to better therapies and prevention strategies for HIV infection and AIDS.

The Planning Process

OAR has established a unique and effective model for developing a consensus on scientific priorities for the annual comprehensive *NIH Plan for HIV-Related Research*. To develop the FY 2007 Plan, OAR sponsored a series of planning workshops to seek the input of non-NIH experts from academia, foundations, industry, and the community. These experts participated with NIH scientific and program staff in Planning Groups for Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; Behavioral and Social Science; Microbicides; HIV Prevention Research; Racial and Ethnic Minorities; Women and Girls; and International Research. Lists of participants in the Planning Groups are found in their respective sections of the FY 2007 Plan. Participants in each Planning Group were asked to review and revise the objectives and strategies of the Plan, based on the state of the science, and to identify a set of priorities for their area. All groups were asked to address needs in Information Dissemination and Training, Infrastructure, and Capacity Building as related to their area. The resulting draft Plan was then provided to each IC Director and AIDS Coordinator for recommendations and comments. Finally, the Plan was reviewed by the Office of AIDS Research Advisory Council (OARAC). A list of current OARAC members is included in Appendix A. OAR continues to reassess the planning process and make refinements in order to better capture the broadest range of scientific expertise and community participation and to facilitate the identification of specific scientific priorities.

Structure of the Plan

The structure of the Plan is designed to comprehensively describe research activities that are needed to address HIV and AIDS, define specific research priorities, and reflect mutual reinforcement among the scientific and crosscutting areas. Each of these sections of the Plan includes (1) Scientific Issues and Priorities and (2) Objectives and Strategies.

Scientific Issues and Priorities: This section provides a scientific overview and specific priorities identified by the Planning Groups. These priorities narrowly define a few key areas deemed most worthy of new or expanded funding based on the current scientific knowledge, opportunities, and gaps. They will be used to guide the development of the FY 2007 AIDS budget and to adjust the FY 2006 AIDS budget as needed.

Objectives and Strategies: This section consists of a comprehensive list of Objectives, in priority order, that address the many needs and challenges within

the field of HIV/AIDS research. Each Objective is followed by a set of Strategies that provide examples of approaches that might be taken to fulfill each Objective. To underscore the interrelationships among areas, strategies may be found under more than one Area of Emphasis.

Uses of the Plan

The Plan serves several important purposes:

- As the framework for developing the NIH AIDS research budget. A chart showing the relationship between the planning and budget process may be found in Appendix B.
- For determining the use of NIH AIDS-designated dollars and for tracking and monitoring those expenditures. The Plan thus defines those research areas for which AIDS-designated funds may be allocated.
- As a document that provides information to the public, the scientific community, Congress, and the AIDS-affected communities about the NIH AIDS research agenda. OAR distributes the annual comprehensive Plan to a wide audience, and it appears on the OAR Web site: http://www.nih.gov/od/oar.

Trans-NIH Comprehensive AIDS Research Budget: The law provides that OAR shall allocate all appropriated AIDS research funds to the Institutes and Centers. The Plan initiates the annual budget development and allocation process. Based on the priorities and objectives established in the Plan, the ICs submit their AIDS-related research budget requests to OAR, focusing on new or expanded program initiatives for each scientific area. OAR reviews the IC initiatives in relation to the Plan, to OAR priorities, and to other IC submissions to eliminate redundancy and/or to ensure cross-Institute collaboration. The NIH Director and the OAR Director together determine the total amount allocated for AIDS research within the overall NIH budget, as required by law. Within that total, OAR allocates the AIDS research budget levels to each IC, based on the scientific priority of the proposed initiatives, at each step of the budget development process up to the time of the final congressional appropriation. This involves consulting regularly with the IC Directors and maintaining knowledge of the ongoing scientific research programs and planned initiatives supported by each IC. This process allows OAR to ensure that NIH AIDS-related research funds will be provided to the most compelling scientific opportunities, rather than distributed simply by a formula. A summary of HIV/AIDS funding by IC for fiscal years 2004-2006 appears in Appendix C.

As congressionally mandated, OAR also prepares an annual "bypass" budget for submission directly to the President. This bypass is essentially a professional judgment budget, based solely on scientific need and opportunity, without regard to cost.

Major Themes of the Plan

The FY 2007 research agenda continues the following overarching themes: a strong foundation of basic science; research to prevent and reduce HIV transmission, including vaccines, microbicides, and behavioral interventions; research to develop better therapies for those who are already infected; international research, particularly to address the pandemic in developing countries; and biomedical and behavioral research targeting the disproportionate impact of AIDS on minority populations in the United States. In particular, this budget request places highest priority on the discovery, development, and preclinical testing of additional HIV vaccine candidates. The evaluation of an AIDS vaccine will require extensive testing in the United States and in international settings where there is a high incidence of HIV. High priority is placed on funding to move promising vaccine candidates into large-scale clinical trials to evaluate the potential for efficacy.

The Plan establishes the NIH AIDS research agenda in the following Scientific Areas of Emphasis: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science. The Plan also addresses the crosscutting areas of: Microbicides; HIV Prevention Research; Racial and Ethnic Minorities; Women and Girls; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination. The key priorities for each research area and directions for future research are summarized below.

NATURAL HISTORY AND EPIDEMIOLOGY

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Sponsor domestic and international epidemiologic investigations into the interactions between HIV genetic variability, host genetics, and other factors that influence disease morbidity and mortality, with special emphasis on different routes of transmission, chronic and infectious comorbidities and malignancies, and long-term use of antiretroviral therapies.**
- **In order to increase the value of different sources of epidemiologic information on HIV/AIDS, develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies of populations experiencing emerging and ongoing HIV epidemics, with particular emphasis on:**
  - **Assessing the short- and long-term effects of preventive and therapeutic interventions at the individual, family, and community levels;**
  - **Establishing integrated databases that allow analyses of large datasets to address new or unresolved scientific questions; and**
  - **Generating new hypotheses regarding the transmission and pathogenesis of HIV infection.**
- **Implement epidemiologic and simulation studies among HIV-infected individuals and appropriate controls to inform, monitor, and evaluate intervention strategies, including initiation of treatment programs, in domestic and international settings.**
- **Continue improving key measures to diagnose and monitor HIV/AIDS in diverse settings by encouraging development of and evaluating late-generation laboratory assays. These include accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; measures of adherence to therapy; and markers of toxicity and comorbidity for use in domestic and international settings.**

Natural history and epidemiologic research is needed to monitor epidemic trends, develop and evaluate prevention modalities, follow the changing clinical manifestations of HIV disease in different populations, and measure the effects of treatment regimens. The NIH will continue to support research to examine topics in HIV transmission, HIV/AIDS disease progression (including the occurrence of opportunistic infections [OIs]), malignancies, metabolic complications, neurological

and behavioral dysfunctions, and the development of other HIV/AIDS-related conditions. Domestically, as well as internationally, the populations affected by HIV/AIDS are also those most severely affected by the spreading epidemics of sexually transmitted diseases (STDs), TB, and other comorbidities, such as hepatitis C. Researchers are studying the effects of viral, host, and other factors on transmission and disease progression. Since biological, pharmacological, psychological, and behavioral factors all potentially influence the impact of antiretroviral therapies on HIV transmission, researchers are evaluating the specific contributions of these factors and their net impact on HIV transmission. Research also is focusing on determining the biological characteristics, sociocultural factors, and health services issues that contribute to the differential dynamics of HIV transmission and disease progression in men, women, and different racial/ethnic groups. Results from these studies will provide new directions and improvements in HIV/AIDS prevention and care. The NIH will continue to emphasize the importance of epidemiologic studies to investigate the mechanisms of disease progression, the causes of death, and the impact of therapy in changing the spectrum of HIV disease. The expansion of existing study populations in the United States will allow the identification of long-term effects of HIV therapy. The assembly of new, representative cohorts, specimen repositories, and databases in developing countries will be important to study key cofactors that modify HIV disease. The NIH will foster basic and applied research to develop inexpensive virologic, immunologic, and genetic assays for use in domestic and developing country settings.

ETIOLOGY AND PATHOGENESIS

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Facilitate the translation of new insights into HIV biology to develop novel interventions for the prevention and treatment of HIV infection. Identify and validate cofactors for viral genes as new targets capitalizing on novel technologies including RNA interference and genomic screening.**
- **Elucidate the biologic determinants of HIV transmission between individuals, and define the mechanisms by which host factors, viral factors, and cofactors may influence the process of HIV transmission and dissemination.**
- **Understand the dynamic of virus-host interaction through the course of HIV infection.**
- **Investigate the mechanisms of persistence of HIV infection.**
- **Develop innovative technologies in human and nonhuman primate immunology to guide HIV prevention and immune reconstitution efforts in HIV-at-risk/infected individuals.**
- **Advance the understanding of the mechanisms responsible for the toxicities and long-term complications of ART and the factors that underlie changes in the causes of morbidity and mortality in HIV-infected patients in an era of increasingly effective therapies.**

Tremendous progress has been made in understanding the fundamental steps in the life cycle of HIV, the host-virus relationship, and the clinical manifestations associated with HIV infection and AIDS. Groundbreaking research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, the methodologies for diagnosis, and the monitoring for efficacy of antiviral therapies. Maintaining a strong commitment to basic research is of paramount importance in our fight against HIV/AIDS. This research is focused on gaining a better understanding in two areas: (1) how HIV infection is established and maintained, and (2) what causes the profound immune deficiency and severe clinical complications that accompany this infection.

Critical questions in this area are: What role do specific HIV proteins play in the viral life cycle in individual cells and within the bodies of infected individuals? What are the primary modes of HIV transmission between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other organ systems affected by HIV? What host factors and cofactors influence primary infection and the course and outcome of HIV

infection? What is the relationship of HIV infection to the associated malignancies, OIs and coinfections, neurological impairments, and metabolic disturbances that characterize AIDS? This basic knowledge is critical for our efforts to prevent and control HIV infection and disease progression.

Research is focusing on the different mechanisms of viral persistence to understand the reasons for drug failure, to design rational approaches for virus eradication, and to better assess the impact of persistence on HIV transmission and its implications for HIV prevention. HIV can persist in a latent reservoir of resting memory CD4 T cells that is established very early after infection and by continuously replicating, albeit at very low levels, even in the presence of antiretroviral therapies that can drive viral load below the limits of detection.

Understanding the normal development and functioning of the human immune system is crucial to our ability to understand the effects of HIV on the immune system and the pathogenesis of AIDS. This understanding also holds the key to designing rational immune reconstitution approaches in persons undergoing antiretroviral treatment and identifying the characteristics of the immune response that are needed for a protective vaccine.

The basic science underlying HIV etiology and pathogenesis research is generally gender neutral. Basic mechanisms of viral replication and pathogenesis are not expected to differ in women and men. However, there are differences in the way HIV infection is transmitted and how the disease is manifested in women and men. Studies have been designed to elucidate the pathogenic mechanisms more commonly observed in women, children, and adolescents infected with HIV. Transmission of HIV from a mother to her infant may occur *in utero* through transplacental passage of virus, during delivery, or after birth through breastfeeding. Many basic research questions associated with maternal-fetal transmission remain unclear and are actively under investigation.

AIDS is associated with a broad spectrum of cancers and tumors. As HIV causes immunosuppression and most AIDS-associated malignancies are strongly associated with viruses, HIV infection provides a unique model to study the interplay of viruses, a dysfunctional immune system, and the development of cancers. Elucidation of the interactive factors involved in the pathogenesis of AIDS-associated malignancies will possibly translate into the identification of new targets for prevention and treatment.

HIV infection results in the progressive damage of the immune systems of infected individuals and makes them susceptible to a diverse collection of bacteria, viruses, fungi, and protozoa that represent the major causes of suffering and death for HIV-infected individuals. Opportunistic infections remain one of the most important

complications of HIV infection and the principal cause of death in AIDS patients. Understanding the fundamental biology and pathogenesis of these organisms, their interaction with the host immune system, and the effect of therapy-associated immune reconstitution on the clinical course and manifestations of OIs will translate into new or more rational approaches to the prevention and treatment of OIs in patients on ART, as well as in patients who lack access to or who are not responding to ART. HIV infection is also associated with multiple endocrine alterations, probably reflecting critical interaction between the endocrine and the immune systems. HIV-associated hematologic, pulmonary, cardiac and vascular, renal, mucocutaneous, bone, and liver complications also represent causes of morbidity in infected subjects. Some of these complications are disproportionally affecting racial groups. The pathogenic mechanisms involved in all these AIDS manifestations are not well understood and are under investigation. Their definition will permit a more rational approach to both preventive and therapeutic interventions.

THERAPEUTICS

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Advance the discovery and validation of new viral and cellular targets. Develop and evaluate new therapeutic agents that: target drug-resistant virus; have activity in viral reservoirs and cellular compartments; and have improved pharmacologic and toxicologic properties.**
- **Determine optimal therapeutic strategies including when to start (early versus late), change, sequence, or interrupt therapies and evaluate therapeutic drug monitoring strategies. Enhance capabilities for long-term followup and evaluate the long-term effects of therapy and the implications of these findings on public health. Identify immunologic correlates of effective viral suppression in the setting of clinical therapeutic intervention trials.**
- **In U.S. settings, target affected populations, especially women, injecting drug users, children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender, age, and/or racial/ethnic differences. In international settings, design and conduct clinical studies to improve and facilitate the delivery of therapeutics and prevention interventions for HIV disease.**
- **Develop safe, effective, feasible, and conveniently administered strategies to interrupt mother-to-child transmission (MTCT) of HIV with a focus on resource-limited settings and a special emphasis on breastfeeding.**
- **Evaluate the effects of short-course antiretroviral (ARV) prophylaxis regimens used for prevention of HIV MTCT on development of drug resistance and the effects of drug resistance on efficacy of prophylaxis, responses to future ART in women and infants who become infected despite prophylaxis, and develop interventions to prevent development of such resistance in women and infected infants. Conduct studies to evaluate and reduce short- and long-term toxicity of ARVs to prevent HIV transmission in women during pregnancy, and in their offspring who were perinatally exposed.**
- **Evaluate interventions, including ARV and immunotherapeutic, in clinical trials to reduce horizontal transmission during both acute and chronic HIV infection. Evaluate the risk of resistance**

to HIV acquisition and transmission during interventional studies designed to reduce horizontal transmission.

- **Evaluate the effects of coinfection, especially with hepatitis B virus (HBV), HCV, TB, Epstein-Barr virus (EBV), or malaria, on the management of HIV. Determine the bidirectional effects of coinfection and treatments on disease progression and drug interactions. Develop new agents for the treatment of HBV, HCV, TB, EBV, and malaria in the setting of HIV infection, with specific attention to pharmacologic drug interactions and nonoverlapping toxicity.**
- **Develop and evaluate therapeutic approaches including vaccines that will improve and sustain immune function and prevent transmission of HIV infection. Identify and validate immunologic determinants to predict the efficacy of immune-based therapies.**

Many HIV-infected people are living with the benefits resulting from NIH-supported therapeutics research. The development of combination regimens including protease inhibitors has extended the length and quality of life for many HIV-infected individuals in the United States and Western Europe. The use of ART continues to result in the significant reduction of viral load, increased CD4 cell counts, decreased OIs and certain malignancies, and improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities associated with antiretroviral drugs. A high priority of NIH-sponsored AIDS therapeutics research continues to be the development of better drugs and therapeutic regimens that are less toxic and have fewer side effects, limit the development of drug resistance, enter viral reservoirs to inhibit viral replication, promote easier adherence, and are more readily accessible. Research is addressing the metabolic complications, including insulin resistance, and body composition changes such as deforming deposits of abdominal adipose tissue, that have emerged in individuals who have been on long-term antiretroviral regimens. More deaths occurring from liver failure, kidney disease, and cardiovascular complications are being observed in this patient population. The global impact and continued spread of the AIDS pandemic in both developed and developing nations underscore the urgent need to develop therapeutic regimens that can be implemented in international settings.

Antiretroviral and OI prophylaxis regimens are becoming increasingly complex with respect to drug-drug interactions and adherence. Protease inhibitors, in particular, interact with each other and many other medications commonly used by HIV-infected individuals. A goal of research is minimizing viral replication and delaying disease progression, drug resistance, and development of clinical complications. Important studies are planned to evaluate delayed and long-term effects of these antiretroviral drugs.

The scientific agenda for NIH AIDS therapeutics research is focused on the following questions: Are there new viral and cellular targets against which therapies can be directed? What therapeutic agents and regimens can be developed that target drug-resistant virus? What are the optimal approaches for management of HIV infection, including when to start, change, sequence, or interrupt therapy? What are the effects of these drugs in pregnant and breastfeeding women, and what impact does this have upon the fetus? What is the impact of coinfection or cancer on disease progression and treatment of both HIV and comorbidities such as hepatitis B virus, hepatitis C virus, tuberculosis, or malaria? What are the clinical and public health ramifications of administering ART in developing countries? Collaboration between Government- and industry-sponsored drug development research and clinical trials is critical to achieve the common goal of developing therapeutic regimens that slow disease progression, extend life spans, and improve the quality of life for HIV-infected individuals.

VACCINES

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Continue to support a broad NIH vaccine research portfolio to ensure a vigorous program of basic and preclinical research for:**
  - **Innovative immunogen design, discovery, preclinical evaluation, and introduction of improved vaccine candidates and immunization concepts. A vigorous pipeline of novel candidates remains a key overarching priority that needs to be balanced with the urgency to develop and test existing HIV vaccine candidates in domestic and international cohorts.**

    The failure of bivalent monomeric recombinant HIV gp120 immunogens to induce responses able to prevent infections in Phase III trials calls for continued emphasis on novel approaches to induce protective antibody responses to HIV envelope. Current candidate HIV vaccine products in development or early testing may provide incremental progress toward this elusive goal. However, further exploration of innovative approaches is still needed to induce high-titered neutralizing antibody responses that are broadly cross-reactive with diverse HIV clades and circulating recombinant forms of HIV.
  - **Detailed analyses of the immune responses generated by vaccine candidates that lead to protective immunity.**
- **Support research on the identification of correlates of immune protection: study the development and maintenance of effective immune responses to HIV antigens, particularly those able to provide protection at mucosal surfaces, address issues related to improvement in the duration of potentially protective immune responses, and develop shared resources for comparative analysis of vaccine candidates.**
- **Using the most efficient and cost-effective designs, conduct clinical trials of HIV vaccine candidates in appropriate human populations. If possible, implement direct "head-to-head" comparative studies of vaccine candidates, but the main effort should be directed to the comparative assessment of immune responses with validated assays and standardized methods for sample handling in both preclinical and clinical evaluation of HIV vaccine candidates to enable comparisons across trials. Appropriate reagents, quality assurance assays, and animal models should be developed. Information, standard operating**

procedures, and reagents should be shared widely to facilitate comparative vaccine studies. To ensure comparability, expanded assessments of cellular immunity and neutralizing antibodies in central laboratories using validated assays and broader access to specimens are encouraged for both academic and industrial investigators.

- **Improve the linkage of vaccine design efforts with the clinical trial networks and cohorts/populations being identified for clinical trials to better integrate preclinical data into human vaccine trial planning and to inform and educate all stakeholders. Conduct appropriate preparative work in trial sites, particularly in international sites and racial and ethnic minority communities, to provide critical viral and immunological information to inform vaccine trial design while helping to develop strong, sustainable research infrastructure and advocacy for HIV vaccines.**

Safe and efficacious vaccines to prevent HIV infection and disease and/or transmission are essential for global control of the AIDS pandemic. As a result of increased funding from the NIH in the area of HIV vaccines, many new approaches are being pursued. Basic research in vaccine design and studies of immune responses in small animals and nonhuman primates (NHP) as well as vaccine product development are underway. Recent HIV vaccine research studies in animal models have provided strong scientific rationales to further explore and develop several vaccine concepts and to move additional candidate vaccines into clinical testing. Although production of candidate vaccines for clinical study has proceeded slowly, at least four to eight new candidate vaccines will enter Phase I trials in the next 2 years. Several new combinations of products, which are expected to provide better immune responses, also will be tested in Phase I or II trials. The Dale and Betty Bumpers Vaccine Research Center recently launched the first Phase I clinical trial of a multiclade, multigene vaccine candidate.

The NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical research on candidate vaccine products. As promising candidates move further in the vaccine pipeline, expanded trials with populations at increased risk for HIV infection will become increasingly important. HIV/AIDS vaccine research requires trained health care, medical research, and prevention specialists, as well as populations at risk who will be integrally involved in the development of vaccine candidates and clinical vaccine and prevention trials. International and domestic sites are being developed, including a cadre of trained personnel, to conduct vaccine trials.

One of the foremost priorities for testing candidate vaccines continues to be a resolution of the crisis in the supply of monkeys available for HIV/AIDS vaccine

studies. The supply of NHP, particularly rhesus macaques, for AIDS research and other areas of biomedical research remains a major problem for NIH-funded investigators. Both the supply of animals and the available space for conducting experiments that require adequately controlled biosafety housing are limiting and impeding exploration of new concepts in HIV vaccines. The NIH is working to find solutions to these obstacles.

The development of an HIV vaccine is a complex research challenge because HIV is unusually well equipped to elude immune defenses, as exemplified by its ability to vary extensively, to persist in viral reservoirs, and to eventually overcome the immune system. Many different vaccine approaches are being pursued. Initial studies are leading to more advanced vaccine candidates that may provide better protection. The NIH has now conducted approximately 70 Phase I and 2 Phase II clinical trials of nearly 40 vaccine candidates, individually or in combination, in human volunteers in collaboration with academic investigators and industry cosponsorship.

BEHAVIORAL AND SOCIAL SCIENCE

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Develop and test the predictive utility of comprehensive models for risk of HIV transmission and acquisition that reflect the complex, multidetermined nature of sexual behavior and the influences that factors distal from the immediate risk behavior have on HIV transmission and acquisition.**
- **Elucidate new and changing patterns, contexts, and kinds of drug and alcohol use and their implications for HIV transmission and acquisition, either directly or as mediators of sexual behavior.**
- **Develop and evaluate methods of intervening to reduce HIV acquisition and transmission associated with sexual behavior, using methods that recognize the contributions and interactions of individual, dyadic, group, community, and societal level (structural) variables, as well as the role of the environment and behavioral implications of technological advances in medicine (e.g., rapid HIV testing, medications to treat sexual dysfunction) and changes in medical practice (e.g., simplified dosing regimens, routine and universal testing).**
- **Develop and evaluate methods of intervening to reduce HIV acquisition and transmission associated with drug and alcohol use, using methods that recognize the contributions and interactions of individual, dyadic, group, community, and societal level variables, as well as the role of the environment and behavioral implications of technological advances in medicine (e.g., partial opiate agonist therapy) and changes in medical practice (e.g., directly observed therapy's integration with drug abuse treatment, increased attention to unique needs of women and ethnic/racial minorities).**
- **Support research on the interactions among factors that contribute to the cooccurrence of HIV/AIDS and other medical disorders (e.g., infectious diseases, substance abuse) and social problems (e.g., homelessness), and develop interventions to address the cooccurring conditions.**
- **Improve understanding of means to rectify disparities in consequences of and care for HIV infection through addressing the needs of various population subgroups and the stigma associated with HIV/AIDS, and through fostering integration of prevention and care services appropriate to both HIV-seropositive and HIV-seronegative persons.**

- **Test, refine, and apply findings from areas of research that are potentially relevant to HIV/AIDS issues, such as operations research, investigations of psychotherapy and behavior change with other medical conditions, management studies, family planning and reproductive health, behavioral economics, medical anthropology/sociology, and others, to determine the applicability of principles and procedures from those research areas and disciplines to HIV/AIDS.**
- **Integrate behavioral and social science expertise in the design and conduct of clinical trials and "strategy trials" of biomedical interventions so that behavioral and social aspects of biomedical interventions, such as acceptability and adherence, are included appropriately and adequately.**

The NIH supports research to further our understanding of how to change the behaviors that lead to HIV transmission—including preventing their initiation—and how to maintain protective behaviors once they are adopted in all populations at risk. The NIH sponsors research related to: developing, implementing, and evaluating behavioral and social interventions to reduce HIV transmission in a range of populations and settings; strengthening our understanding of the determinants, trends, and processes of HIV-related risk behaviors and the consequences of HIV infection; developing and evaluating behavioral strategies for preventing or ameliorating the negative physical, psychological, and social consequences of HIV infection; and improving the methodologies employed in behavioral and social science research. A better understanding of social and cultural factors associated with HIV risk or protection, particularly in minority communities, will contribute to the successful implementation of a broader range of preventive or therapeutic measures. Drug users and their sex partners are the fastest growing segment of AIDS cases in the United States and in many other countries. Priority is being given to research that bridges and builds upon studies of the phenomenon of addiction itself, the complex interaction of alcohol use, drug use, and poor impulse control, and to developing effective HIV-related interventions from that knowledge base.

The development of new and more effective anti-HIV drugs and drug combinations has raised a host of behavioral issues. Lack of complete adherence to drug regimens may result in the development of drug-resistant strains of HIV, which could have devastating public health implications. In addition, HIV-infected individuals taking antiretroviral therapies who experience improved health and a decline in detectable virus may believe that they are less infectious and may lapse into unsafe sexual and drug-using behaviors. This could have the effect of increasing HIV transmission, if the virus is still viable at undetectable levels. These issues highlight the importance of research on how best to ensure adherence to both pharmacological and behavioral HIV-related interventions.

MICROBICIDES

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Foster the development of single and combination microbicides consisting of a variety of potential agents, both chemically and biologically derived, that are based on their specific biological and physiological properties and have the potential to interact with the pathways involved in HIV transmission across the epithelia.**
- **Identify and standardize relevant, practical, and accessible methodologies to assess preclinical/clinical safety and activity of microbicides.**
- **Foster the development of combination approaches and of microbicides containing multiple active compounds with different chemical classes, specificities, and mechanisms of action in acceptable formulations to prevent transmission and acquisition of HIV and other sexually transmitted infections (STIs).**
- **Promote innovative methods to develop and assess acceptable formulations and modes of delivery for microbicides against HIV, bridging knowledge and applications from multiple scientific disciplines.**
- **Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase I/II/III microbicides clinical trials.**
- **Conduct social and behavioral research in concert with microbicides clinical trials, including research on product use, user acceptability, sexual behaviors, and the identification and development of reliable and valid behavioral tools and measurement techniques for use in trials.**
- **Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on microbicides discovery and development.**

The vulnerability of women to acquiring HIV infection requires the development of effective and acceptable female-controlled chemical and physical barrier methods, such as topical microbicides, to reduce HIV transmission. The NIH supports a comprehensive research program that includes the screening, discovery, development, preclinical *in vitro* and *in vivo* testing, and clinical evaluation of compounds with the potential to act as antimicrobial agents with both spermicidal and nonspermicidal activity. The NIH closely collaborates with academia and industry to identify and explore new and existing compounds as potential topical microbicidal agents.

The Office of AIDS Research coordinates microbicide research across the NIH, with other Federal agencies providing administrative accountability and funding coordination for this important research area.

Animal model testing and toxicity studies of potential candidate compounds are conducted through NIH-sponsored contracts before these agents are considered for clinical trials. The NIH also supports Phase I, II, and III clinical trials of various topical microbicides, as well as behavioral and social research on the acceptability and use of microbicides among different populations. Important areas of research include the establishment of clinical trial sites and the necessary infrastructure to conduct those trials, especially in developing countries; the development of criteria for selecting potential products to be evaluated in clinical trials and for advancing them through the different phases of clinical studies; and research on ethical and behavioral issues impacting clinical trials.

HIV PREVENTION RESEARCH

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Examine how social, economic, cultural, and environmental conditions, including stigma and discrimination, contribute to, or create sources of, HIV-related risk, and develop interventions based on this understanding.**
- **Examine and address the factors associated with the initiation and sustainability of HIV prevention efforts among individuals and communities over time, as well as the underlying problems (e.g., depression, substance abuse) that may impede the adoption of consistent HIV risk-reduction practices, and develop innovative strategies to address them.**
- **Elucidate the prevention-treatment interface, including the effects of HIV/AIDS treatment availability, delivery, success, and failure on HIV transmission and acquisition, and the integration of prevention into clinical care.**
- **Further explore, develop, and evaluate alternative methods to the randomized controlled trial (RCT) for testing the efficacy of multidisciplinary HIV preventive interventions when RCTs are inappropriate or impossible to conduct, and develop guidelines to inform the field about when such non-RCT methods are appropriate to employ.**
- **In collaboration with other governmental and nongovernmental organizations, enhance support for operations, health services, and evaluation research on the design, adaptation, testing, and implementation of evidence-based HIV prevention strategies, and assess the impact of such strategies on risk behaviors at the population level.**

The NIH supports a comprehensive prevention science research agenda that targets interventions to both infected and uninfected at-risk individuals to reduce HIV transmission. Biomedical prevention research priorities include the development of topical microbicides, strategies to prevent MTCT (including a better understanding of HIV risk associated with breastfeeding), and management of STDs. NIH behavioral research strategies include interventions related to drug and alcohol use and risky sexual behaviors. Research efforts continue to identify the most appropriate intervention strategies for different populations and subepidemics in the United States and around the world.

These HIV prevention research activities include both basic and intervention studies. Research that elucidates the fundamental mechanisms of human behavior and disease transmission and progression provides the essential basic knowledge needed for the development of testable interventions. Studies examine the range and interaction of biological, neurological, psychological, familial, social network, and other environmental factors that have an impact on HIV transmission, acquisition, or protection. While the focus of the NIH HIV prevention research program is on primary prevention of new HIV infections, it also addresses secondary prevention, that is, prevention of the negative physiological, psychological, and social consequences of disease among individuals already infected with HIV and their families, networks, and communities. This includes identifying potential cofactors, correlates, and mediators of disease progression, and developing biomedical and/or psychosocial interventions to address them.

RACIAL AND ETHNIC MINORITIES

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Include racial and ethnic minorities in numbers that reflect their level of risk as well as their representation in the HIV epidemic. Examining their risk trajectory in the incident data can best assess this level of risk.**
- **Enhance the capacity of minority investigators, minority institutions, and minority community-based organizations to conduct multidisciplinary research. As one of a number of health disparities, HIV infection and the reduction of its transmission within racial and ethnic minority communities must be addressed by those within, as well as outside of, those communities.**
- **Identify biomedical, sociocultural, psychosocial, and structural determinants, pathways, and mechanisms that maintain or perpetuate health disparities. It is essential to examine these determinants in the context of social structure and to use ecological models to explore these pathways.**
- **Develop and test innovative models, research methods, and measures of risk behavior in racial and ethnic minority communities. Existing models and methods do not reflect the cultural and social context of the lives of racial and ethnic minorities, especially Native Americans and Alaska Natives.**
- **Identify and address the impact, as well as the specific and unique aspects, of HIV infection upon Native American and Alaska Native communities, with particular attention to the epidemiologic, sociocultural, and psychosocial antecedents and effects. Further exploration and enhancement of mechanisms to identify, train, mentor, and develop Native American and Alaska Native investigators is a critical component of response to HIV infection in these communities.**
- **Examine the effectiveness of therapeutic interventions in racial and ethnic minorities as well as adherence to therapeutic regimens within the sociocultural context of the populations affected. This approach must include the examination of traditional health and healing practices and their role in acceptance of HIV therapeutic interventions in these communities.**
- **The NIH, in conjunction with other U.S. Department of Health and Human Services (DHHS) agencies, must review its mission and**

approach to the HIV epidemic to identify and address through specific mechanisms the barriers that are created by maintenance of discrete, mutually exclusive approaches to the epidemic without significant interagency collaborations. These barriers have the unintended consequence of restricting the ability of racial and ethnic minority investigators and communities to address the unique and often interdisciplinary aspects of HIV infection. This continues to foster a fragmented response that interferes with effective "real world" community responses and intervention.

HIV infection, like many other disease states, reflects the ongoing health disparities among racial and ethnic minority communities. Prevalence of HIV infection in racial and ethnic minority communities is disproportionately higher than in majority communities. In many U.S. urban centers, the prevalence of HIV infection mimics rates found in the developing world. These findings, along with the resurgence of STDs and associated high-risk behaviors, underscore the need for comprehensive strategies to decrease HIV transmission in affected vulnerable populations, and improve treatment options and treatment outcomes.

The NIH is directing increased resources toward research to develop new interventions that will have the greatest impact on these groups. These include interventions that address the cooccurrence of other STDs, hepatitis, drug abuse, and mental illness; and interventions that consider the role of culture, family, and other social factors in the transmission and prevention of these disorders in minority communities. The NIH is making significant investments to improve research infrastructure and training opportunities for minorities and will continue to ensure the participation of minorities in AIDS clinical trials, as well as in natural history, epidemiologic, and prevention studies. The NIH has provided additional funds to projects aimed at increasing the number of minority investigators conducting behavioral and clinical research; targeting the links between substance abuse, sexual behaviors, and HIV infection; increasing outreach education programs targeting minority physicians and at-risk populations; and expanding the portfolio of population-based research. One of these projects is a series of Training and Career Development Workshops for racial and ethnic minority investigators. These workshops provide minority investigators with an opportunity to learn more about available NIH funding mechanisms and to meet and network with senior minority investigators who receive significant levels of NIH funding.

The NIH supports a broad array of behavioral intervention studies with specific focus on African American populations. These studies are characterizing the disease process in drug users, factors influencing disease progression, consequences of multiple coinfections, effectiveness of therapeutic regimens, and the impact of health care access and adherence to therapeutic regimens on disease outcomes. The

increasing number of AIDS cases among minorities underscores the importance of research to define and utilize cultural, social, and contextual factors that affect HIV risk behaviors. The role of alcohol and drug use in facilitating HIV transmission through social networks in all communities also is being explored within these social frameworks.

WOMEN AND GIRLS

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Study the biology of the reproductive tract and mucosal surfaces of HIV-infected and HIV-uninfected women and girls, integrating studies of physiology, pharmacology, immunology, microbiology, and anatomy in order to clarify mechanisms of HIV transmission, acquisition, and disease progression.**
- **Elucidate a range of innate and acquired host characteristics and viral interactions through the course of HIV infection (in particular, during primary HIV infection and response to treatment) across the life cycle in women and girls.**
- **Develop and continue domestic and international clinical studies—biological, therapeutic, vaccine, natural history, epidemiological, behavioral, and social—to ascertain the effects of sex and gender in HIV infection and response to treatment among women and girls.**
- **Power clinical trials to identify sex and gender differences.**
- **Explore factors that influence development, adoption, use, and effectiveness of women-controlled methods (including physical and chemical barrier methods), alone or in combination, for preventing HIV transmission and acquisition.**
- **Integrate basic behavioral and social science research (theoretical and methodological) on gender construction, maintenance, dynamics, and consequences—including gender-based stigma and discrimination—into the design and evaluation of HIV prevention and care interventions.**
- **Enhance opportunities and mechanisms for recruiting and training biomedical, behavioral, and social scientists in the conduct of interdisciplinary and multidisciplinary HIV/AIDS research in women and girls, addressing women's health issues and analyzing sex and gender differences, and facilitate development of the infrastructure to support such research.**

Women experience HIV/AIDS differently from men both physiologically and socially. NIH research has demonstrated that women progress to AIDS at lower viral load levels and higher CD4 counts than do men. This finding may have implications for care and treatment of HIV-infected women, particularly with antiretroviral therapy. Women's childbearing capacity also differentiates their HIV/AIDS experiences from men's, as HIV-infected pregnant women may transmit the virus to their fetuses and infants. Women in most societies are the primary care

providers for children and older people, so their early deaths from AIDS and its complications often leave dependents with no one to care for them. NIH researchers are studying the ways in which sex and gender confer vulnerability to, or protection from, HIV infection and AIDS among women and girls—in general, and relative to men—in diverse geographical settings and during different stages of the life course. There are many research questions that remain unanswered about specific anatomical and physiological characteristics of women and girls that might play a role in transmission, acquisition, or resistance to HIV infection. Studies will focus on factors in HIV acquisition, including the influence of hormonal modulation on viral replication and immune responses in the reproductive tract, and cofactors, such as coincident infections with other STD pathogens.

INTERNATIONAL RESEARCH

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- **Develop in-country HIV/AIDS research training and research infrastructure.**
- **Conduct research to identify a comprehensive set of effective, appropriate, and sustainable interventions to curtail HIV transmission, including a combination of approaches at multiple levels to target existing and emerging at-risk populations.**
- **Conduct both experimental and observational research to identify appropriate care and treatment strategies to limit the impact of HIV-related disease.**
- **Conduct research to examine the interactions among aspects of treatment and prevention, including the impact of therapy on the HIV epidemic.**

Since the early days of the epidemic, the NIH has supported research efforts in countries affected by HIV and AIDS. Beginning in 1984 with a research project in Haiti and the establishment of Projet SIDA in 1985 in what was then Zaire, the NIH has maintained a strong international AIDS research portfolio. The NIH has expanded its research effort to encompass approximately 90 countries around the world. Results of this research benefit not only the people in countries where the research is conducted, but people affected by HIV/AIDS worldwide. NIH-sponsored international research includes efforts to develop: HIV vaccine candidates and chemical and physical barrier methods, such as microbicides, to prevent sexual transmission; behavioral strategies targeted to the individual, family, and community to alter risk behaviors associated with sexual activity and drug and alcohol use; drug and nondrug strategies to prevent MTCT; therapeutics for HIV-related coinfections and other conditions; and approaches to using ART in resource-poor settings.

Before prevention and treatment interventions can be implemented in different geographic settings, their safety must be confirmed and efficacy demonstrated in such settings through clinical trials and other intervention research. To develop vaccines and other prevention strategies that will be effective globally, Phase I safety studies are first conducted in small populations in the United States To establish efficacy, large numbers of at-risk study participants are necessary. Around the world, the predominant mode of HIV transmission is heterosexual. Among heterosexuals in the United States, the rate of HIV infection is estimated to be approximately 1.5 percent. In some developing countries, the rate of heterosexual HIV infection is 13-25 percent. Because of the large populations at high risk of infection, prevention studies can be more efficiently conducted in those settings.

Although industrialized nations have experienced a dramatic decrease in transmission of HIV from infected mother to her child, preventing this transmission is a significant challenge in resource-poor settings of the world; strategies that can effectively be used in such settings continue to be pursued.

Development of a research infrastructure is essential to these research programs. Specific international infrastructure needs include: (1) developing research sites through establishment of stable, targeted cohorts, development of recruitment strategies, and enhancement of laboratory, clinical, and data management capabilities; (2) increasing the number of scientists, clinicians, and health care workers trained in basic, clinical, and behavioral research, data management, and ethical considerations; (3) developing research collaborations; and (4) transferring appropriate clinical and laboratory technologies.

Training, Infrastructure, and Capacity Building

The NIH will continue to support training of domestic and international biomedical and behavioral AIDS researchers, as well as the improvement of facilities and equipment for the conduct of AIDS-related research, including facilities for animal model research. Numerous NIH-funded programs have increased the number of training positions for AIDS-related research, including programs specifically designed to recruit individuals from minority communities into research careers and to build research infrastructure in minority institutions. The NIH Loan Repayment Program (LRP) was mandated by Congress under Public Law 100-607 in 1988 and authorized under 42 USC 288-1 to encourage health professionals to engage in AIDS-related research at the NIH. The NIH also sponsors programs to train scientists in developing countries to undertake AIDS research. The National Primate Research Centers (NPRC) Program provides specialized facilities, scientific and technical personnel, animal models research and breeding, and a wide variety of nonhuman primate species to support diverse requirements for AIDS-related research.

Information Dissemination

Effective information dissemination approaches will continue to be integral to HIV prevention and treatment efforts. Such programs are critical in light of the continuing advent of new and complex antiretroviral treatment regimens, the adherence issues related to HIV/AIDS treatment, the need for research communities to work and communicate globally, and the need to translate behavioral and social prevention approaches into practice. The changing pandemic and the increasing number of HIV infections in specific population groups, such as minorities and women, also underscore the need to disseminate HIV research findings and other related information to communities at risk. The flow of information among researchers,

health care providers, and the affected communities represents new opportunities to rapidly translate research results into practice and to shape future research directions.

AIDS Research Benefits Other Research

AIDS research is unraveling the mysteries surrounding many other infectious, malignant, neurologic, autoimmune, and metabolic diseases. AIDS research has provided an entirely new paradigm for drug design, development, and clinical trials to treat viral infections. For example, the drug known as 3TC, developed to treat HIV/AIDS, is now the most effective therapy for chronic hepatitis B infection. Drugs developed to prevent and treat AIDS-associated opportunistic infections also provide benefit to patients undergoing cancer chemotherapy or receiving anti-transplant-rejection therapy. AIDS research also is providing a new understanding of the relationship between viruses and cancer.